REMARKS

Claims 1-27 are pending in the present application; claims 15-23 are withdrawn from consideration. Reconsideration is respectfully requested.

Formalities

The Eidenmuller reference that reportedly was not received by the Examiner is enclosed herewith. Consideration of this reference is requested.

The 35 U.S.C. § 112, 2nd Paragraph Rejections

The Examiner alleges that claims 1-14 and 24-27 are indefinite. Applicants traverse.

Claim 1

Applicants have amended claim 1 to include a comparison step and to clarify that the recited amino acid residues are "of the proteins," as suggested by the Examiner (Office action, page 2, paragraph (5)a)).

Applicants disagree with the Examiner's allegation that claim 1 is indefinite because the phosphorylation states of the "one or more proteins" being compared could be the same or different proteins (Office action, page 2, paragraph (5)(b)). As the Examiner has recognized, the recited method is not limited to comparing the phosphorylation states of the same protein rather than different proteins (or visa versa) in two or more samples. However, "[b]readth of a claim is not to be equated with indefiniteness." MPEP § 2173.04. The lack of a limitation to comparing phosphorylation states of the same protein is not necessary for one of ordinary skill in the art to understand what is being claimed. This rejection is improper.

Applicants also disagree with the Examiner's allegation that claim 1 is indefinite because it is allegedly unclear whether the "two or more samples" are being treated together or separately (Office action, page 2, paragraph (3)). It would be clear to one of ordinary skill in the art that the samples are treated separately because the claim recites that each sample is reacted with *one* of the protein reactive reagents. This rejection is improper.

Applicants further disagree with the Examiner's allegation that claim 1 is indefinite because the recitation of "the capture reagent" is allegedly unclear (Office action, page 3,

paragraph (5)). However, Applicants have amended claim 1 to clarify that a different capture reagent can be used with each sample.

Applicants additionally disagree with the Examiner's allegation that claim 1 is indefinite because the purpose of the steps of "capturing" and "releasing" is allegedly unclear (Office action, page 3, paragraph (6)). The Examiner's confusion as to the purpose of steps in the recited method does not render claim 1 indefinite. In fact, the Examiner essentially admits that these steps are definite by stating what she believes the steps do (Office action, page 3, paragraph (6)). This rejection is improper. To satisfy the Examiner's curiosity, however, the Examiner may wish to review the disclosure in the second paragraph of page 5.

Applicants also disagree with the Examiner's allegation that claim 1 is indefinite because the recitation of "formerly phosphorylated" is allegedly unclear (Office action, page 3, paragraph (7)). Far from being unclear, this recitation means just what it says, that is, that the phosphate reactive group reacts with amino acid residues that once had a phosphate group, but no longer do. This rejection is improper.

Accordingly, Applicants request that the Examiner withdraw each of the § 112 rejections of claim 1.

Claim 4

In view of the comparison step now present in amended claim 1, the Examiner's concern with respect to the recitation of "amount" in claim 4 is now moot.

Accordingly, Applicants request that the Examiner withdraw the § 112 rejection of claim 4 (Office action, page 3, paragraph (8)).

Claims 7 and 8

Applicants have amended claims 7 and 8 to recite "in one or more of the two or more samples" for consistency with claim 1.

Accordingly, Applicants request that the Examiner withdraw the § 112 rejections of claims 7 and 8 (Office action, page 3, paragraph (9)).

Claim 9

Applicants have amended claim 9 to clarify that the two or more samples are combined prior to the capturing process and have deleted the "measuring relative abundances" language the Examiner alleged was nonsensical (Office action, page 3, paragraph (10)).

Applicants disagree with the Examiner's allegation that claim 9 is indefinite because the phosphorylation states of the "one or more proteins" being compared could be the same or different proteins (Office action, page 2, paragraph (5)(b)). As, discussed above, the recited method is not limited to comparing the phosphorylation states of the same protein rather than different proteins (or visa versa) in the two or more samples and claim breadth does not render a claim indefinite. Accordingly, Applicants request that the Examiner withdraw the § 112 rejections of claim 9.

Claim 12

Applicants disagree with the Examiner's allegation that claim 12 is indefinite because the recitation of "at different times" is allegedly unclear (Office action, page 3, paragraph (11)). However, Applicants have amended claim 12 to clarify that the different samples contain proteins that are expressed at different times in the specimen from which the samples are taken.

Accordingly, Applicants request that the Examiner withdraw the § 112 rejection of claim 12.

Claim 24

Applicants have amended the detecting step of claim 24 to clarify that amino acid residues are detected, as is consistent with the preamble (Office action, page 3, paragraph (12)).

Applicants also have amended claim 24 to include the step of providing one or more samples, which provides an antecedent basis for "each sample" (Office action, page 3, paragraph (13)).

Applicants disagree with the Examiner's allegation that the recitation of "differentially isotopically labeled protein reactive reagents" is indefinite (Office action, page 3, paragraph (14)). Applicants have, however, amended claim 24 to clarify that the reagents used to tag the at

least one tyrosine reside are differentially isotopically labeled relative to the protein reactive reagents used to tag the at least one serine residue.

Accordingly, Applicants request that the Examiner withdraw the § 112 rejections of claim 24.

35 U.S.C. § 102(a) Rejections

Claims 1-13

The Examiner alleges that claims 1-13 are anticipated under 35 U.S.C. § 102(a) by published U.S. Patent Application No. 2002/0049307 to Aebersold et al., and published Patent Cooperation Treaty (PCT) application WO 00/11208 also to Aebersold et al. Applicants traverse.

102(e)

As a preliminary matter, Aebersold's published U.S. application is not prior art under 35 U.S.C. § 102(a). This application was published on April 25, 2002, which is after Applicants' filing date of February 16, 2001. Accordingly, its disclosure may not be applied against Applicant's claims under § 102(a).

Aebersold's published PCT application does not anticipate claim 1. Independent claim 1 recites "amino acid residues that were formerly phosphorylated." Aebersold does not disclose the removal of phosphate groups. Therefore, Aebersold's published PCT application does not disclose each and every element of claim 1. A claim is not anticipated unless each and every element set forth in the claim is found in a single prior art reference. MPEP § 2131.

For at least the reasons discussed above, claim 1 is not anticipated by Aebersold's published PCT application and is allowable over the art of record. Claims 2-13 are allowable at least because they depend from allowable claim 1.

Accordingly Applicant's request the Examiner withdraw the § 102(a) rejections of claims 1-13.

Claim 14

The Examiner alleges that claim 14 is anticipated under 35 U.S.C. § 102(a) by Aebersold's published U.S. application and published PCT application. Applicants traverse.

As discussed above, Aebersold's published U.S. application is not prior art under 35 U.S.C. § 102(a) and its disclosure cannot be applied against Applicant's claims under § 102(a).

Aebersold's published PCT application does not anticipate claim 14. Claim 14 recites "removing one or more phosphate groups from one or more amino acid residues." Aebersold's published PCT application does not teach or suggest the removal of phosphate groups from one or more amino acid residues. Therefore, Aebersold's published PCT application does not anticipate claim 14.

For at least the reasons discussed above, claim 14 is allowable over the art of record.

Accordingly Applicant's request the Examiner withdraw the § 102(a) rejection of claim 14.

35 U.S.C. § 103(a) Rejections

Claims 24-27

The Examiner alleges that claims 24-27 are unpatentably obvious under 35 U.S.C. §103(a) in view of Aebersold's published U.S. application and Aebersold's published PCT application in combination with U.S. Patent No. 5,686,310 to Haystead et al. Applicants traverse.

As mentioned above in relation to § 102(a), Aebersold's published U.S. Application was published and filed after Applicants' filing date. It is not prior art and may not be applied against Applicant's claims for the purposes of § 103(b).

Aebersold's published PCT application (hereafter "Aebersold") does not teach or suggest the removal of phosphate groups, as is recited in claim 24. In fact, Aebersold teaches away from the removal of phosphate groups by teaching the use of groups that "*react with* . . . phosphate reactive groups" as the protein reactive groups of Aebersold's disclosed affinity tags. (Page 15, line 3) (emphasis added).

Applicants note that the Examiner equates Applicants' "phosphate reactive groups" with the groups entitled "phosphate reactive groups" in Aebersold at line 3 of page 15. (Office action, page 4, paragraph (8)). These groups are not equivalent.

Aebersold refers to a phosphate functional group on a target protein (where phosphate is used an adjective to explain that the reactive group on the protein is a phosphate). This is evidenced by the fact that Aebersold teaches a protein reactive group that *reacts with* protein functional groups such as the "phosphate reactive group" of a protein. (Page 14, line 26 – page 15 line 3). In contrast, Applicants' phosphate reactive group included in Applicants' protein reactive group is not a phosphate functional group on a protein. For example, Applicants disclose numerous phosphate reactive groups that are not phosphate groups, such as primary, secondary, and tertiary amines. (Application page 11; see also pages 12-13). Rather, Applicants recited phosphate reactive group is a group that reacts with an amino acid where a phosphate group has been removed (i.e., formerly phosphorylated). Applicants use the term phosphate reactive group to refer to a group that can react with a formerly phosphorylated amino acid residue, not to recite that the group is a protein's phosphate functional group.

In light of the comments above, it is clear that Aebersold neither teaches nor suggests a component equivalent to Applicants' "phosphate reactive groups" (as recited in claim 24).

Further, as Aebersold does not teach or suggest the removal of phosphate groups, it also does not teach or suggest tagging amino acid residues with differentially isotopically labeled regents having phosphate reactive groups that selectively react with amino acid residues that were formerly phosphorylated, as is also recited in claim 24.

Haystead does not make up for the deficiencies of Aebersold.

Haystead does not teach or suggest the removal of a phosphate group from threonine, as is recited in claim 24. In fact, Haystead teaches away from removal of phosphate groups from threonine. Haystead states, "the work using phosphothreonine protein showed a lack of threonine participation in the alkaline β-elimination reaction at the reaction conditions stated." (Column 6, lines 18-23).

Additionally, as stated by the Examiner (Office action, page 5, paragraph (9)), Haystead does not teach or suggest tagging amino acid residues with differentially isotopically labeled regents as recited in claim 24. Rather, Haystead teaches, in general, the addition of fluorescent tags to derivatized peptides. (E.g., column 3, lines 30-45).

None of the art or record, either independently or in combination, teaches or suggests Applicants' method recited in claim 24. For at least the reasons discussed above, claim 24 is allowable. Claims 25-27 are allowable at least because they depend from allowable claim 24.

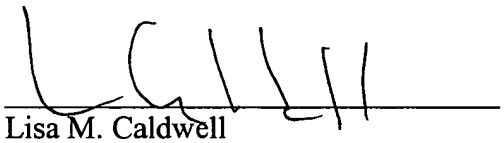
Accordingly Applicants request the Examiner withdraw the § 103(a) rejections of claims 24-27.

Conclusion

Based on the foregoing, Applicants submit that all pending claims are allowable and that this application is in condition for allowance. Should the Examiner believe that anything further is necessary to put this application in better condition for allowance, the Examiner is requested to contact the undersigned by telephone.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 

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Marked-up Version of Amended Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

In the Claims

Claims 1, 7-9, 12, and 24 have been amended as follows.

1. (Once Amended) A method of comparing the phosphorylation states of one or more proteins in two or more samples comprising:

providing a substantially chemically identical and differentially isotopically labeled protein reactive reagent for each sample wherein the protein reactive reagent satisfies the formula:

B-L-PhRG

wherein B is a binding agent [that selectively binds to a capture reagent (CR)], L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that selectively reacts with amino acid residues of the one or more proteins that were formerly phosphorylated;

reacting each sample with one of the protein reactive reagents to provide proteins bound to the protein reactive reagent, whereby such bound proteins are differentially labeled with stable isotopes;

capturing bound proteins of the samples using [the] a capture reagent that selectively binds the binding agent of the protein reactive reagent;

releasing captured bound proteins from the capture reagent by disrupting the interaction between the binding agent and the capture reagent; [and]

detecting the amount of released bound proteins[.]; and

comparing the amount of released bound proteins from one sample to the amount of released bound proteins from one or more other samples.

7. (Once Amended) The method of claim 1, wherein a plurality of proteins [in a single sample] are detected and identified in one or more of the two or more samples.

8. (Once Amended) The method of claim 3, wherein all of the proteins in [a] one or more of the two or more samples [sample] are identified.

9. (Once Amended) The method of claim 1, wherein [relative amounts of one or more proteins in two or more samples are determined and further comprising] the two or more samples are combined after being reacted with a protein reactive reagent and before the bound proteins of the samples are captured [combining differentially labeled samples, capturing bound proteins from the combined samples and measuring relative abundances of the bound proteins differentially labeled proteins].

12. (Once Amended) The method of claim 9, wherein [different samples represent] each of the two or more samples are taken at different times, or contain proteins expressed in response to different environmental or nutritional conditions, or different chemical or physical stimuli [or at different times].

24. (Once Amended) A method of detecting different types [more than one type] of phosphorylated amino acid residues [residue] in [a] one or more proteins [protein], the method comprising:

providing one or more samples containing one or more proteins;

removing the phosphate group from at least one serine residue or at least one threonine residue of at least one protein in each sample;

removing the phosphate group from at least one tyrosine residue of at least one protein in each sample;

tagging the at least one serine residue or the at least one threonine residue with substantially chemically identical and differentially isotopically labeled protein reactive reagents for each sample, wherein the protein reactive reagents satisfies the formula:

B-L-PhRG

wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and

PhRG is a phosphate reactive group that selectively reacts with amino acid residues that were formerly phosphorylated;

tagging the at least one tyrosine residue with substantially chemically identical and differentially isotopically labeled protein reactive reagents for each sample, which are differentially isotopically labeled relative to the protein reactive reagents used to tag the at least one serine residue of the at least one threonine residue, wherein the protein reactive reagents satisfies the formula:

B-L-PhRG

wherein B is a binding agent that selectively binds to a capture reagent, L is a linker group having one or more atoms that are differentially labeled with one or more stable isotopes, and PhRG is a phosphate reactive group that selectively reacts with amino acid residues that were formerly phosphorylated; and

detecting the tagged [protein] amino acid residues.